METHODS OF PRODUCTION, AND PHARMACEUTICAL USES THEREOF

The difference between the new Title and the previously pending Title is shown in the marked-up copy of the Title attached hereto.

In the Claims

Please amend claims 5, 14, 23 and 50 and add new claims 55-72 under the provisions of 37 C.F.R. §1.121(c). The amended set of claims is presented below and the amendments to the claims are indicated in the marked-up set of claims attached hereto.

5. (Amended) A composition comprising a substantially homogeneous crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, and a carrier.

14. (Amended) A method of treating abnormal cell growth in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim 1.

23. (Amended) A method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim 1 in combination with an anti-tumor agent selected from the group consisting of a mitotic

Sub C6 B3

inhibitor, an alkylating agent, an anti-metabolite, an intercalating antibiotic, a growth factor inhibitor, a cell cycle inhibitor, an enzyme, a topoisomerase inhibitor, a biological response modifier, an anti-hormone, and an anti-androgen.

50. (Amended) A method for prophylaxis against the development of basal or squamous cell carcinoma of the skin in areas exposed to the sun or in persons of high risk to said carcinoma, said method comprising administering to said persons a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and pharmaceutically acceptable salts thereof in anhydrous and hydrate forms, so as to thereby result in prophylaxis against the development of basal or squamous cell carcinoma of the skin.

B4 Sub C8

Please add new claims 55-72 as follows:

55. (New) A composition comprising a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91 in a weight % of the B polymorph relative to the A polymorph which is at least 70%.

B5

B

56. (New) The composition of claim 55, wherein the B polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately:

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	1.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	4.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	1.4	35.737	0.8
12.483	6.4	20.196	14.4	25.138	10.0	29.797	2.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.6	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	2.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	2.4	38.114	1.7

57. (New) The composition of claim 55, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in Figure 3.

58. (New) A pharmaceutical composition which comprises a therapeutically effective amount of the polymorph of claim 1 and a pharmaceutically acceptable carrier.

59. (New) The pharmaceutical composition of claim 58, wherein said composition is adapted for oral administration.

60. (New) The pharmaceutical composition of claim 59, wherein the pharmaceutical composition is in the form of a tablet.

61. (New) A method for the production of a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph by recrystallization comprising the steps of:

a) heating to reflux alcohol, water and the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine so as to form a solution;

b) cooling the solution to between about 65 and 70 °C;

c) clarifying the solution; and

d) precipitating polymorph B by further cooling the clarified solution.

62. (New) A composition comprising a substantially homogeneous crystalline polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the form of polymorph B, which is characterized by the following peaks:

Polymorph B

Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity:0.500)

Range # 1 - Coupled 3.000 to. 40.040 StepSize: 0.040 StepTime 1.00

Smoothing Width: 0.300 Threshold: 1.0

d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)
14.11826	100.0	5.01567	2.5	3.86656	4.8	3.23688	0.9	2.74020	1.7
11.23947	3.2	4.87215	0.7	3.76849	2.3	3.16755	1.5	2.69265	1.7
9.25019	3.9	4.72882	1.5	3.71927	3.0	3.11673	4.3	2.58169	1.5
7.74623	1.5	4.57666	1.0	3.63632	6.8	3.07644	1.4	2.51043	0.8
7.08519	6.4	4.39330	14.4	3.53967	10.0	2.99596	2.1	2.47356	1.0
6.60941	9.6	4.28038	4.2	3.47448	3.7	2.95049	0.9	2.43974	0.6
5.98828	2.1	4.20645	14.4	3.43610	3.9	2.89151	1.6	2.41068	1.1
5.63253	2.9	4.06007	4.7	3.35732	2.8	2.83992	2.2	2.38755	1.4
5.22369	5.5	3.95667	4.5	3.31029	5.6	2.81037	2.4	2.35914	1.7

or,

Polymorph B

Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity:0.500)

Range# 1 - Coupled: 3.000 to 40.040 StepSize 0.040 StepTime: 1.00

Smothing Width:0.300 Threshold: 1.0

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	1.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	4.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	1.4	35.737	0.8
12.483	6.4	20.196	14.4	25.138	10.0	29.797	2.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.6	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	2.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	2.4	38.114	1.7

63. (New) A method of inducing differentiation of tumor cells in a tumor comprising contacting the cells with an effective amount of the compound of claim 1, or a composition of claims 3 or 6 so as to thereby differentiate the tumor cells.

64. (New) A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), melanoma, Barrett's esophagus (pre-malignant syndrome), adrenal and skin cancers and auto immune, neoplastic cutaneous diseases and atherosclerosis in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and pharmaceutically acceptable salts thereof in anhydrous and hydrate forms.

65. (New) The method of claim 64, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.

26 66. (New) The method of claim 24, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).

27 67. (New) The method of claim 24, for use in treatment of tumors that express EGFRvIII.

28 68. (New) The method of claim 24, wherein the treatment further comprises a combination with any of chemotherapy and immunotherapy.

BS 29 69. (New) The method of claim 24, wherein the treatment further comprises, treatment with either or both anti-EGFR and anti-EGF antibodies.

Sub E1 30 70. (New) The method of claim 24, wherein the treatment further comprises a further administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metallo-proteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, $CTLA_4$.(cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 Mab.

31 71. (New) The method of claim 24, wherein the pharmaceutical compounds are used as radiation sensitizers for cancer treatment or in combination with anti-hormonal therapies.

32 72. (New) The method of claim 24, wherein the pharmaceutical compounds are used for the inhibition of tumor growth in humans in a regimen with radiation treatment.